Making the causal link: frontal cortex activity and repetition priming

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Object identification improves with repeated presentation, but neural activity decreases. In a new study, disrupting inferior frontal activity with transcranial magnetic stimulation during initial exposure to an object blocks later behavioral and neural changes.

As we all know, many things are easier the second time around. That includes object identification, which is faster and more efficient when we see an object for the second time. This behavioral phenomenon, termed repetition priming, is one of the most interesting and actively investigated forms of memory[1]. Priming is preserved in patients who, as a result of medial temporal lobe damage, are unable to consciously retrieve objects they have seen before. However, although repetition improves performance, on the neural level, priming is typically associated with decreased activity[2]. This paradoxical coupling of reduced neural activity with improved behavior has attracted considerable interest, as investigators have attempted to forge direct links between changes at the behavioral and neural levels. Imaging studies show significant correlations between neural decreases in specific brain regions and priming[3,4]. However, as with all brain imaging studies, this relationship is necessarily indirect because it is based solely on correlation. Thus, whether decreased neural activity causes priming has remained very much an open question. Now, by using transcranial magnetic stimulation (TMS) to transiently perturb neural processing, Wig and colleagues in this issue[5] provide evidence for a causal link between decreased activity and priming.

The Wig *et al.* study involved three phases. In the first phase, the neural system associated with priming was identified using event-related fMRI (functional magnetic resonance imaging). To accomplish this goal, subjects were shown a series of object pictures before scanning and asked to classify each conceptually as living or non-living. They were then scanned while performing the same conceptual task on already seen (repeated) objects, as well as on new objects. As expected, both behavioral priming (faster classification of repeated objects), and 'neural priming' (less neural activity for repeated objects) were observed. In agreement with previous reports[6], neural priming was seen throughout nearly all brain regions associated with the processing of common visual objects, including bilateral portions of the occipital lobe associated with perceptual processing and left posterior temporal and inferior frontal regions associated with conceptual processing (**Fig. 1**).

The second phase of the experiment took place approximately one week later. TMS was administered while subjects made living/non-living judgments on a new set of objects. The left inferior frontal cortex was chosen as the primary site of interest on the basis of its involvement in conceptual processing, and TMS was applied here during the presentation of some objects. TMS was also applied to a control site—the hand region of left motor cortex—during presentation of the other objects. Importantly, TMS administration was tailored for each subject in two ways. A frameless stereotaxic system was used to allow the investigators to place the TMS probe directly over the point in the subject's inferior frontal cortex that showed the largest repetition effect in the first, scanning phase. The investigators also used the subject's behavioral performance from the first phase to begin administering TMS approximately 250 ms before each subject's typical response time.

TMS did not prevent subjects from performing the task accurately, regardless of the site of administration. The investigators then evaluated the impact of TMS on

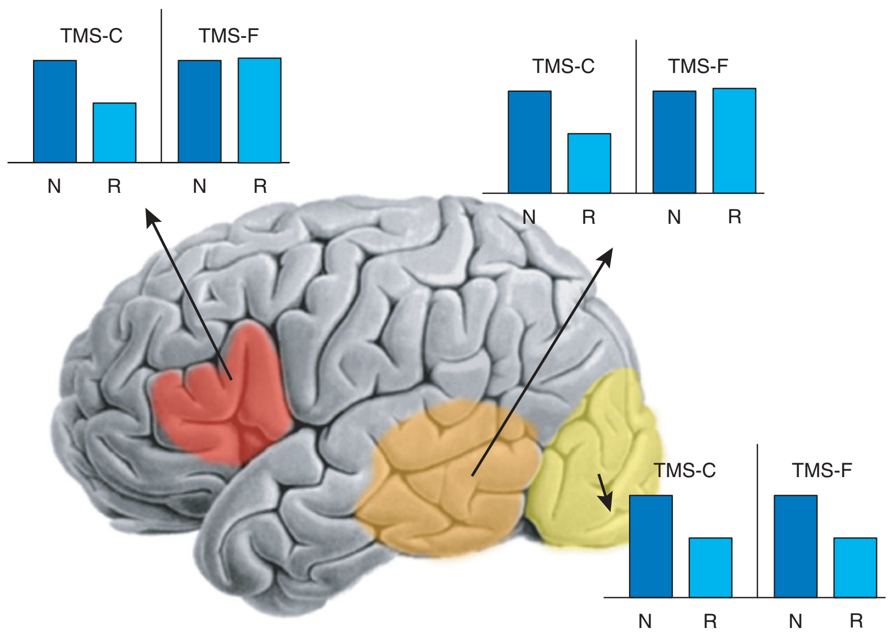

Figure 1 Summary of the neuroimaging findings. After control TMS was applied to left motor cortex (TMS-C), reduced activity in response to repeated (R) compared to novel (N) objects ('neural priming') was observed in regions associated with visual (occipital cortex, yellow) and conceptual (temporal, orange) object processing, and in the left inferior frontal cortex (red), associated with conceptual and lexical processing and selection. After TMS was applied to left inferior frontal cortex (TMS-F), behavioral priming was eliminated, as was neural priming in left inferior frontal and temporal cortices, but not in occipital cortex. The common pattern of neural priming in frontal and temporal cortices suggests a functional interaction between these two regions.

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both behavioral and neural priming in a final scanning phase a few minutes later. The logic here is that because priming is presumed to result from events triggered during the initial processing (encoding) of an object, the consequences of TMS during encoding should be observable at a later time. During scanning after TMS, subjects again performed the same living/non-living task either on objects previously encoded during TMS or on new objects.

The findings were clear and striking. Behavioral priming was eliminated for objects encoded during TMS of left inferior frontal cortex, but not for objects encoded during stimulation of left motor cortex. Moreover, priming-related neural activity decreases were eliminated, but only in certain brain regions. Activity decreases were maintained in regions of occipital cortex known to be associated with visual processing of object features, whereas decreases were not observed in either left inferior frontal cortex (the TMS site) or left posterior temporal cortex (**Fig. 1**). These results demonstrate a causal role for left inferior frontal cortex in at least one form of repetition priming. They also demonstrate a link between decreased neural activity and priming. Nevertheless, these two phenomena could be dissociated. Repetition-related decreases continued to occur in occipital cortex even when behavioral priming was absent.

The Wig *et al.* study[5] is a *tour de force* with regard to the logic of its design and execution. To accomplish the authors' goal required multiple behavioral and functional imaging sessions and the individual tailoring of TMS administration with regard to both site and timing of stimulation. As a result of their efforts, we now have evidence from the normal human brain of a causal relationship between the neural and behavioral aspects of priming. It is noteworthy, as well, that their finding converges nicely with those of fMRI correlational studies showing a stronger coupling between behavioral and neural priming in left inferior frontal than in posterior cortices[3,4], thus suggesting that we are on the right track.

Nevertheless, many important issues remain to be resolved. First, converging evidence is needed from patients with focal left inferior frontal lesions (Broca's aphasics). Broca's aphasics show intact priming on some procedures, but not on others[7,8]. However, in contrast to the study by Wig *et al.*, the priming procedure used in these studies have been markedly different with regard to stimuli (words rather than pictures) and task. Based on the Wig *et al.* finding, we would expect that the ability of these patients to classify object pictures as living or non-living would not improve with repetition. This possibility needs to be confirmed.

Several other predictions can be made. The procedure used by Wig *et al.* is a version of conceptual repetition priming[9]. The main features of this procedure are that the same object is presented at study and test and that the orienting task used at study and at test is conceptual—requiring a decision based on the meaning of the object—rather than perceptual. From a processing point of view, the task requires engagement of visual processing mechanisms largely located in occipital cortices[10], access to conceptual object information largely stored in temporal cortices[11] and engagement of left inferior frontal mechanisms for selecting and retrieving this information[12]. Viewed within this framework, one of the more intriguing aspects of the Wig *et al.* results is the lack of neural priming in left posterior temporal cortex induced by left inferior frontal TMS. Considerable neuropsychological and neuroimaging evidence suggests left posterior temporal cortex is critically involved in conceptual processing of objects, perhaps because information about object category–related properties is stored there[11]. For subjects to accurately classify the objects as living or nonliving requires access to the conceptual information represented in this region of the brain. The Wig *et al.* finding suggests that this information is accessed through the top-down influence of left inferior frontal cortex and that behavioral priming is mediated by the interaction of these two regions. As a result, TMS to left posterior temporal region should show effects similar to those demonstrated for inferior frontal TMS: behavioral priming and neural priming in left posterior temporal and frontal cortex, but not occipital cortex, should be eliminated.

But what about occipital cortex? In the Wig *et al.* study, neural priming was maintained in this brain region. One possible explanation for this finding is that perceptual priming is independent of the modulatory influence and control of frontal lobe mechanisms. A different possibility is that TMS applied to frontal cortex could eliminate neural priming in occipital cortex if the orienting task were focused more exclusively on visual dimensions (for instance, a task requiring a difficult visual form discrimination).

Another important issue that remains to be explored is the effect of inferior frontal TMS on other forms of object memory. As the authors state, after TMS, subjects responded to the repeated presentations of the objects as if they were seeing them for the first time. However, would explicit memory be similarly impaired? Although there is abundant evidence showing that priming and explicit memory can be dissociated, TMS to inferior frontal cortex during encoding may disrupt both forms of memory, especially because the amount of left inferior frontal cortex activity during encoding is a strong predictor of whether an item will be later remembered[13]. The procedure developed by Wig *et al.* could be used to directly test the effects of inferior frontal TMS at encoding for both priming and remembering.

A final major puzzle remains. Wig. *et al.* have shown that disrupting one part of the circuitry that typically shows neural priming can disrupt behavioral priming. Nevertheless, how repetition-related decreases in neural activation cause behavioral facilitation is still unknown. To resolve this vexing question will require a clearer understanding of mechanism(s) producing repetition-related decreases in neural activity in different regions of the brain[2,14,15].

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